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Signed Stephen Hordley

Dated 8 November 2004

Patents Form 1/77

Patents Act 1977
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04NOV03 E849168-1 C90116
P01/7700 0.00-0325644.3

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

51/MG

2. Patent application number
(The Patent Office will fill this part in)

0325644.3

- 4 NOV 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AVIDEX LTD
57C MILTON PARK
ABINGDON
OXFORDSHIRE OX14 4RX

Patents ADP number *(if you know it)*

8571242001

If the applicant is a corporate body, give the country/state of its incorporation

ENGLAND

4. Title of the invention

IMMUNO IHIBITORY PYRAZOLONE COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

MR ALAN WALLS
AVIDEX LTD
57C MILTON PARK
ABINGDON
OXFORDSHIRE OX14 4RX

Patents ADP number *(if you know it)*

8480618001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

YES

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

	Continuation sheets of this form
Description	28 —
Claim(s)	4 — & 3
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	NONE
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Alan M Walls Date 03/11/03

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

MR ALAN WALLS (01235) 438600

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

Immuno Inhibitory Pyrazolone Compounds

The present invention relates to pyrazolone compounds, to methods for their preparation, to compositions containing them, and to methods and use for clinical treatment of medical conditions which may benefit from immunomodulation, e.g. rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis. More particularly the present invention relates to pyrazolone compounds, which are CD80 antagonists capable of inhibiting the interactions between CD80 and CD28.

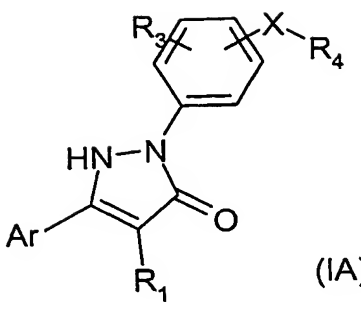
Background to the Invention

The immune system possesses the ability to control the homeostasis between the activation and inactivation of lymphocytes through various regulatory mechanisms during and after an immune response. Among these are mechanisms that specifically inhibit and/or turn off an immune response. Thus, when an antigen is presented by MHC molecules to the T-cell receptor, the T-cells become properly activated only in the presence of additional co-stimulatory signals. In the absence of these accessory signals there is no lymphocyte activation and either a state of functional inactivation termed anergy or tolerance is induced, or the T-cell is specifically deleted by apoptosis.

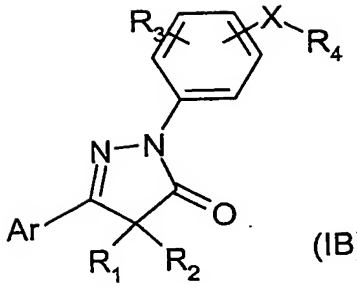
One such co-stimulatory signal involves interaction of CD80 on specialised antigen-presenting cells with CD28 on T-cells, and this signal has been demonstrated to be essential for full T-cell activation. (Lenschow *et al.* (1996) *Annu. Rev. Immunol.*, **14**, 233-258). It would therefore be desirable to provide compounds which inhibit this CD80/CD28 interaction.

Detailed Description of the Invention

According to the present invention there is provided a compound of formula (IA) or (IB) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof:



(IA)



(IB)

wherein

Ar represents an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group having from 5 to 10 ring atoms,

R_1 and R_2 independently represent H, or C_1-C_6 alkyl;

R_3 represents H; F; Cl; Br; -NO_2; -CN; C_1-C_6 alkyl optionally substituted by F or Cl; or C_1-C_6 alkoxy optionally substituted by F;

R_4 represents a carboxylic acid group (-COOH) or an ester thereof, or –C(=O)NR_6R_7, -NR_7C(=O)R_6, -NR_7C(=O)OR_6, –NHC(=O)NR_7R_6 or –NHC(=S)NR_7R_6 wherein

R_6 represents H, or a radical of formula –$(Alk)_m$-Q wherein

m is 0 or 1

Alk is an optionally substituted divalent straight or branched C_1-C_{12} alkylene, or C_2-C_{12} alkenylene, or C_2-C_{12} alkynylene radical or a divalent C_3-C_{12} carbocyclic radical, any of which radicals may be interrupted by one or more –O-, -S- or –N(R_8)- radicals wherein R_8 represents H or C_1-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl, or C_3-C_6 cycloalkyl, and

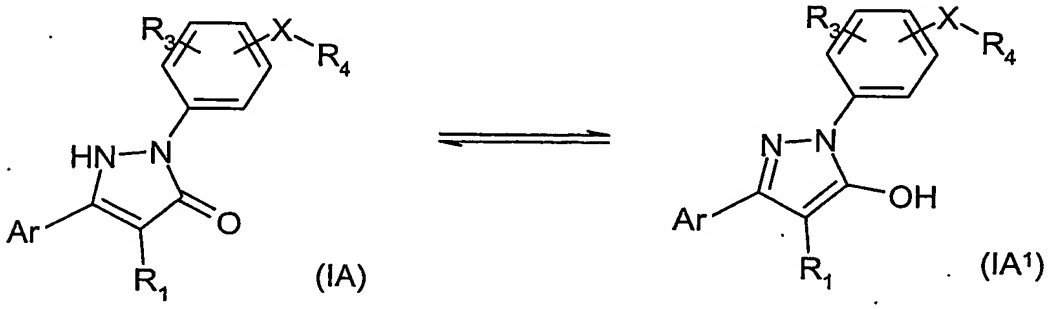
Q represents H; -CF_3; -OH; -SH; -NR_8R_8 wherein each R_8 may be the same or different, or form a ring when taken together with the nitrogen to which they are attached; an ester group; or an

optionally substituted aryl, aryloxy, cycloalkyl, cycloalkenyl or heterocyclic group; and

R_7 represents H or C_1-C_6 alkyl; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form a monocyclic heterocyclic ring having 5, 6 or 7 ring atoms; and

X represents a bond or a divalent radical of formula $-(Z)_n-(Alk)-$ or $-(Alk)-(Z)_n-$ wherein Z represents –O-, -S- or –NH-, Alk is as defined in relation to R_6 and n is 0 or 1.

Compounds (IA) may exist in the form of tautomers (IA^1):



Hereafter, the compounds (IA) of the invention may be represented and referred to in either tautomeric form and it is to be understood that any and all tautomeric forms of structures (IA) and (IB), in particular (IA^1), are included in the invention.

Compounds of general formula (IA) and (IB) are CD80 antagonists. They inhibit the interaction between CD80 and CD28 and thus the activation of T cells, thereby modulating the immune response.

Accordingly the invention also includes:

(i) a compound of formula (IA) or (IB) or a pharmaceutically or veterinarily acceptable salt thereof for use in the treatment of conditions which benefit from immunomodulation.

(ii) the use of a compound of formula (IA) or (IB) or a pharmaceutically or veterinarily acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which benefit from immunomodulation,.

(iii) a method of immunomodulation in mammals, including humans, comprising administration to a mammal in need of such treatment an immunomodulatory effective dose of a compound of formula (IA) or (IB) or a pharmaceutically or veterinarily acceptable salt thereof.

(iv) a pharmaceutical or veterinary composition comprising a compound of formula (IA) or (IB) or a pharmaceutically or veterinarily acceptable salt thereof together with a pharmaceutically or veterinarily acceptable excipient or carrier.

Conditions which benefit from immunomodulation include:

Acute disseminated encephalomyelitis
Adrenal insufficiency
Allergic angiitis and granulomatosis
Amylodosis
Ankylosing spondylitis
Asthma
Autoimmune Addison's disease
Autoimmune alopecia
Autoimmune chronic active hepatitis
Autoimmune haemolytic anaemia
Autoimmune Neutrogena
Autoimmune thrombocytopenic purpura
Behçet's disease
Cerebellar degeneration
Chronic active hepatitis
Chronic inflammatory demyelinating polyradiculoneuropathy
Chronic neuropathy with monoclonal gammopathy
Classic polyarteritis nodosa
Congenital adrenal hyperplasia

Cryopathies
Dermatitis herpetiformis
Diabetes
Eaton-Lambert myasthenic syndrome
Encephalomyelitis
Epidermolysis bullosa acquisita
Erythema nodosa
Gluten-sensitive enteropathy
Goodpasture's syndrome
Guillain-Barre syndrome
Hashimoto's thyroiditis
Hyperthyroidism
Idiopathic hemachromatosis
Idiopathic membranous glomerulonephritis
Isolated vasculitis of the central nervous system
Kawasaki's disease
Minimal change renal disease
Miscellaneous vasculitides
Mixed connective tissue disease
Multifocal motor neuropathy with conduction block
Multiple sclerosis
Myasthenia gravis
Opsoclonus-myoclonus syndrome
Pemphigoid
Pemphigus
pernicious anaemia
Polymyositis/dermatomyositis
Post-infective arthritides
Primary biliary sclerosis
Psoriasis
Reactive arthritides
Reiter's disease
Retinopathy
Rheumatoid arthritis

Sclerosing cholangitis
Sjögren's syndrome
Stiff-man syndrome
Subacute thyroiditis
Systemic lupus erythematosis
Systemic necrotizing vasculitides
Systemic sclerosis (scleroderma)
Takayasu's arteritis
Temporal arteritis
Thromboangiitis obliterans
Type I and type II autoimmune polyglandular syndrome
Ulcerative colitis
Uveitis
Wegener's granulomatosis

As used herein, the term "ester" refers to a group of the form –COOR, wherein R is a radical notionally derived from the alcohol ROH. Examples of ester groups include the physiologically hydrolysable esters such as the methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, and benzyl esters.

As used herein the term "alkylene" refers to a straight or branched alkyl chain having two unsatisfied valencies, for example $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2CH_3)CH_2CH_2CH_2-$, and $-C(CH_3)_3$.

As used herein the term "alkenylene" refers to a straight or branched alkenyl chain having two unsatisfied valencies, for example $-CH=CH-$, $-CH_2CH=CH-$, $-C(CH_3)=CH-$, and $-CH(CH_2CH_3)CH=CHCH_2-$.

As used herein the term "alkynylene" refers to a straight or branched alkynyl chain having two unsatisfied valencies, for example $-C\equiv C-$, $-CH_2C\equiv C-$, and $-CH(CH_2CH_3)C\equiv CCH_2-$.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent, for example selected from (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy (including the special case where a ring is substituted on adjacent ring C atoms by alkylenedioxy such as methylenedioxy or ethylenedioxy), trifluoromethoxy, (C_1-C_6)alkylthio, phenyl, benzyl, phenoxy, benzyloxy, hydroxy, mercapto, amino, fluoro, chloro, bromo, cyano, nitro, oxo, -COOH, $-SO_2OH$, $-CONH_2$, $-SO_2NH_2$, $-COR^A$, $-COOR^A$, $-SO_2OR^A$, $-NHCOR^A$, $-NHSO_2R^A$, $-CONHR^A$, $-SO_2NHR^A$, $-NHR^A$, $-NR^AR^B$, $-CONR^AR^B$ or $-SO_2NR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl or C_2 – C_6 alkoxy group or a monocyclic carbocyclic or heterocyclic group of from 5-7 ring members, or R^A and R^B form a ring when taken together with the nitrogen to which they are attached. In the case where "substituted" means substituted by phenyl, benzyl, phenoxy, or benzyloxy, the phenyl ring thereof may itself be substituted with any of the foregoing, except phenyl, benzyl, phenoxy, or benzyloxy.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and to two such radicals covalently linked to each other, Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the unqualified term "carbocyclyl" or "carbocyclic" includes aryl, cycloalkyl and cycloalkenyl and refers to a ring system (monocyclic, bicyclic, tricyclic or bridged) whose ring atoms are all carbon.

As used herein the unqualified term "cycloalkyl" refers to a carbocyclic ring system which contains only single bonds between ring carbons.

As used herein the unqualified term "cycloalkenyl" refers to a carbocyclic ring system which contains at least one double bond between a pair of ring carbons.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and

O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a mono-, bi- or tri-cyclic or bridged non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

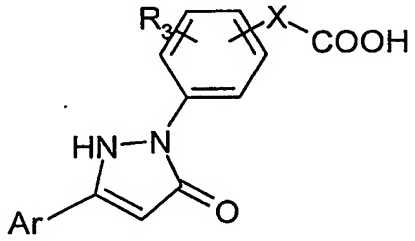
Some compounds of the invention contain one or more chiral centres because of the presence of asymmetric carbon atoms. The presence of asymmetric carbon atoms gives rise to stereoisomers or diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such stereoisomers and diastereoisomers and mixtures thereof.

Salts of salt forming compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates; and base addition salts, for example sodium, potassium, magnesium, and calcium salts.

Methods

Compounds of the invention of formula (IA) wherein R_1 is hydrogen and wherein R_4 represents an amide group

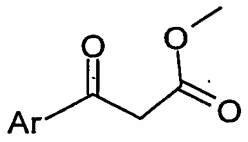
$-C(=O)NR_6R_7$ may be prepared by reaction of the appropriate amine HNR_6R_7 with a compound of formula (II) to amidate the carboxylic acid group:



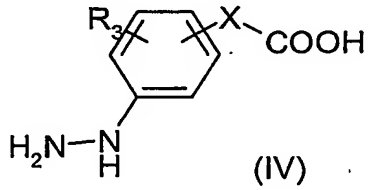
(II)

the symbols Ar, R_3, X, R_6 and R_7 being as defined in relation to formula (I) above.

Compounds (II) (ie compounds (IA) of the invention wherein R_1 is hydrogen and R_4 is a carboxylic acid group) may be prepared by reaction of a compound of formula (III) with a hydrazine of formula (IV):

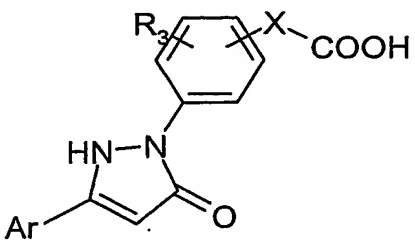


(III)

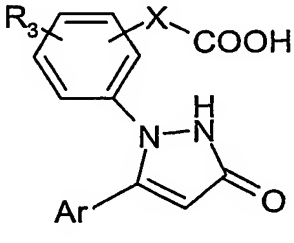


(IV)

This reaction may result in the preparation of a mixture of the position isomers (IIA) and (IIB):



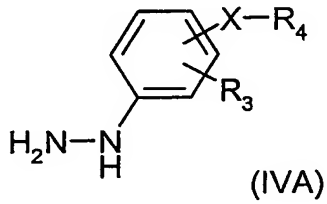
(IIA)



(IIB)

from which the desired isomer (IIA) may be separated.

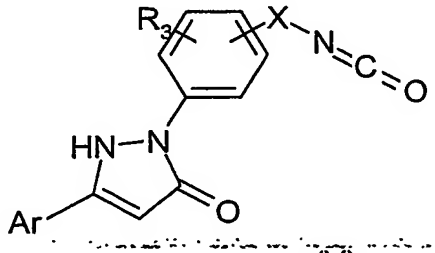
Compounds (IA) wherein R_1 is hydrogen and R_4 is an amide ($-C(=O)NR_6R_7$) or ester group may also be prepared from intermediate (III) by reaction with the appropriate hydrazine (IVA)



(IVA)

wherein R_4 is the amide or ester group. Again the reaction may result in a mixture of the ester analogues of the carboxylic acids (IIA) and (IIB), from which the desired ester isomer (I) may be separated. Alternatively, the carboxylic acid compound (II) may simply be esterified, or amidated (the latter being a route referred to above).

Compounds (IA) wherein R_1 is hydrogen and R_4 is a "reverse amide" group - $NR_7C(=O)R_6$ may be prepared by Curtius rearrangement (see Ninomiya, K.; Shioiri, T.; Yamada, S. Tetrahedron (1974), 30(14), 2151-7) of the carboxylic acid (II) to the isocyanate (V)



(V)

followed by hydrolysis of the isocyanate group to an amino group and acylation of the amino group with, for example, the acid chloride Cl-$C(=O)R_6$. In cases where R_7 is not hydrogen, the R_7 substituent may be introduced after the isocyanate reduction step or after the acylation step.

Compounds (IA) wherein R_1 is hydrogen and R_4 is a urea group – $NHC(=O)NHR_6$ or thiourea group $-NHC(=S)NHR_6$ may also be prepared from

the isocyanate (V) or the corresponding isothiocyanate by reaction with the appropriate amine H_2NR_6.

Compounds (I) wherein R_4 is a carbamate group $-NR_7C(=O)OR_6$ may be prepared by the reaction of the isocyanate with an appropriate alcohol R_6OH.

Compounds (IA) and (IB) wherein R_1 and R_2 are C_1-C_6 alkyl may be prepared by alkylation of the corresponding compound (IA) wherein R_1 is hydrogen.

Further details of the synthetic methods for the preparation of compounds (I) of the invention, and intermediates such as (III), may be found in the examples herein.

In the compounds of the invention:

R_1 and R_2 independently represent hydrogen or C_1-C_6 alkyl, such as methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl.

R_4 represents a carboxylic acid group (-COOH) or an ester thereof, or $-C(=O)NR_6R_7$, $-NR_7C(=O)R_6$, $-NR_7C(=O)OR_6$ or $-NHC(=O)NHR_6$, all as defined above.

When R_4 is an ester group, examples include those of formula –COOR wherein R is methyl, ethyl n- or iso-propyl, n-, sec- or tert-butyl; or benzyl ester.

R_6, when present, represents H, or a radical of formula $-(Alk)_m$-Q wherein m, Alk and Q being as defined above. When m is 1, Alk may be, for example a straight or branched C_1-C_6 alkylene radical, such as $-CH_2$-, $-CH_2CH_2$-, $-CH_2CH_2CH_2$-, and $-CH_2CH(CH_3)CH_2$-. Alk may also be, for example, a divalent cyclopropylene, cyclopentylene or cyclohexylene radical. The radical Alk may be optionally substituted by, for example, OH, oxo, CF_3, methoxy or ethoxy. The radical Alk may

optionally contain a hetero atom, for example in the form of an ether, thioether or amino linkage.

The group Q may represent, for example, hydrogen; -NR_8R_8 wherein each R_8 may be the same or different and selected from hydrogen, methyl, ethyl, n- or isopropyl or tert-butyl; an ester group for example a methyl, ethyl or benzyl ester; or an optionally substituted aryl, aryloxy, cycloalkyl, cycloalkenyl or heterocyclic group, for example phenyl, phenoxy, cyclopentyl, cyclohexyl, furyl, thienyl, piperidyl, or piperazinyl group.

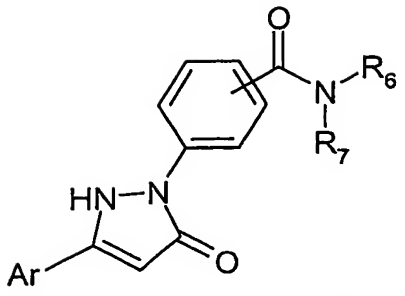
R_7 when present represents H or C_1-C_6 alkyl, for example methyl, ethyl n- or iso-propyl, n-, sec- or tert-butyl; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form a monocyclic heterocyclic ring having 5, 6 or 7 ring atoms;

Ar may be, for example, optionally substituted phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-furyl, 2-, or 3-thienyl, benzfur-2-yl, or benzthien-2-yl. Optional substituents in Ar include, for example F, Cl, methyl, methoxy, or methylenedioxy. Currently it is preferred that Ar is 3-fluorophenyl and 2-, or 3-furyl,

R_3 may be, for example, H, F, Cl, methyl, methoxy, or methylenedioxy. Currently it is preferred that R_3 is H;

X may be, for example a bond, or a $-CH_2-$ or $-CH_2CH_2-$ radical. A bond is presently preferred.

A specific preferred subset of compounds of the invention has formula (IC):



((IC)

wherein Ar, R_6 and R_7 are as specified above. In this subset, the radical $-C(=O)NR_6R_7$ may be in the 4-position of the phenyl ring. This subset includes in particular, compounds wherein R_7 is hydrogen and R_6 is $-AlkNR_8R_8$ wherein the R_8 groups are is as defined above.

Specific compounds of the invention include those of the Examples herein.

As mentioned above, the invention includes pharmaceutical or veterinary composition comprising a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof together with a pharmaceutically or veterinarily acceptable excipient or carrier. In such compositions, it will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the cause and severity of the particular disease undergoing therapy. Optimum dose levels and frequency of dosing will be determined by clinical trial.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example

lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

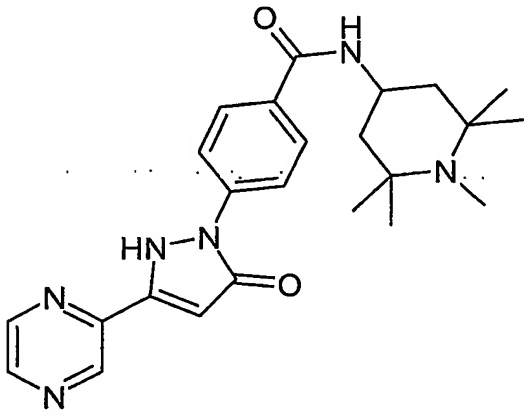
Embodiments of the invention are described in the following non-limiting Examples:

The following abbreviations are used in the experimental descriptions:

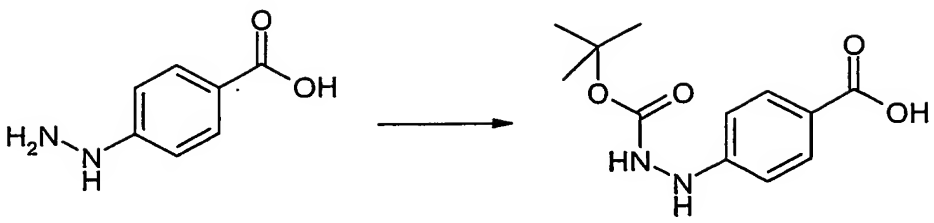
DMF	Dimethyl formamide
DMA	Dimethyl acetamide
DMSO	Dimethyl sulphoxide
THF	Tetrahydrofuran
HBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	High performance liquid chromatography
LCMS	Liquid chromatography mass spectrum
NMR	Nuclear magnetic resonance spectroscopy

Example 1

4-(5-Oxo-3-pyrazin-2-yl-2,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide

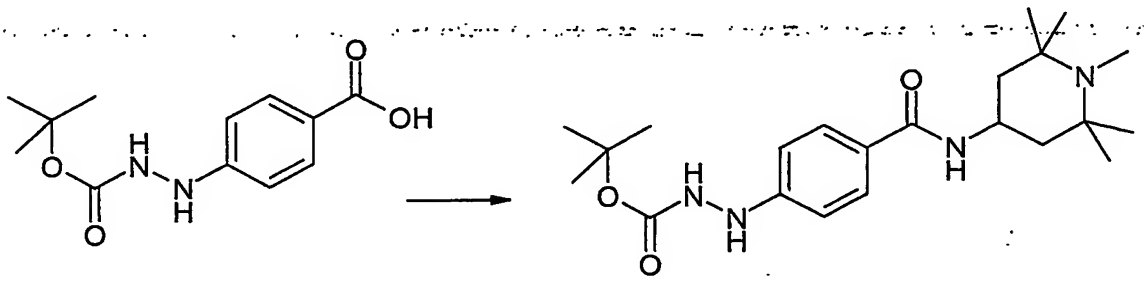


Step 1: Preparation of 4-(N'-tert-Butoxycarbonyl-hydrazino)-benzoic acid



To a deep red solution of p-hydrazinobenzoic acid (32.86 mmol, 5.00 g) in 2M NaOH (100 ml) and THF (70 ml) was added di-*tert*butyl dicarbonate (2.0 eq, 65.72 mmol, 14.34 g). This was stirred at rt over a weekend. Another aliquot of di-*tert*butyl dicarbonate (3.5 g) was added to the reaction mixture, and this stirred at room temp for a further 24 hours. A further 0.5 eq p-hydrazinobenzoic acid added to the reaction mixture. This was then stirred for a further 24 hours. 10% citric acid solution was added until a pH of 4 was obtained. The product was then extracted with ethyl acetate, the organics washed with brine, and then dried over Na_2SO_4. Concentration *in vacuo* afforded a pale yellow oil, containing residual tert-BuOH. Hexane was added to the mixture. Precipitation was observed and the solids were collected by filtration, washed with hexane and dried under vacuum at 35°C. An orange powder was obtained (8.40 g).

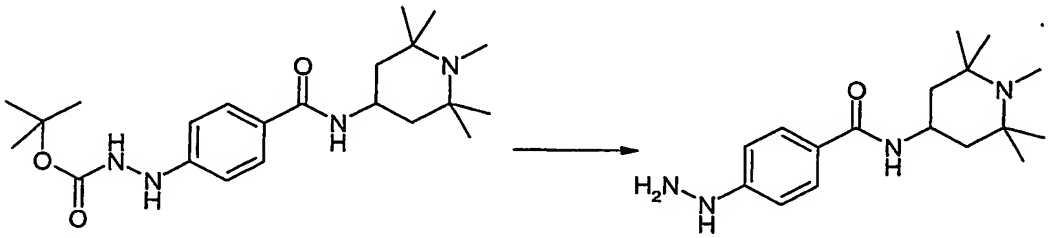
Step 2: Preparation of N'-[4-(1,2,2,6,6-Pentamethyl-piperidin-4-ylcarbamoyl)-phenyl]-hydrazinecarboxylic acid tert-butyl ester



To a solution of 4-(N'-tert-Butoxycarbonyl-hydrazino)-benzoic acid (4.452g) in DMA (30ml) was added disopropyl ethyl amine (6.16ml) and HBTU (6.69g) with stirring at room temp. 4-Amino-1,2,2,6,6-pentamethylpiperidine (3g) was then added to the stirred solution. Stirring continued at room temp for 4hrs.

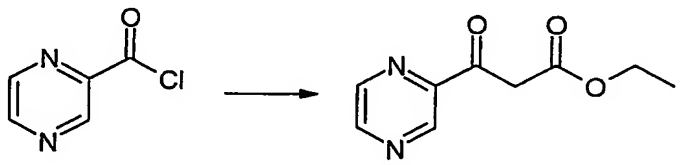
The solution was partitioned between ethyl acetate (6 X 20 ml) and water. The organic fraction was taken, washed with brine, dried over $MgSO_4$ and the solvent removed under vacuum. This revealed a deep orange oil (6.2g, 86%).

Step 3: Preparation of 4-Hydrazino-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide



N'-[4-(1,2,2,6,6-Pentamethyl-piperidin-4-ylcarbamoyl)-phenyl]-hydrazinecarboxylic acid tert-butyl ester was dissolved in 4M HCl in dioxane (30ml) and left to stir for 1-2hrs. The solution went quickly from a deep orange colour to a bright orange colour. After 1hr reaction time, the solvent was removed under vacuum to reveal an orange oil that under a vacuum for several minutes crystalised out to give orange crystals in a sticky orange oil. Yield: 4.68 g, 87%.

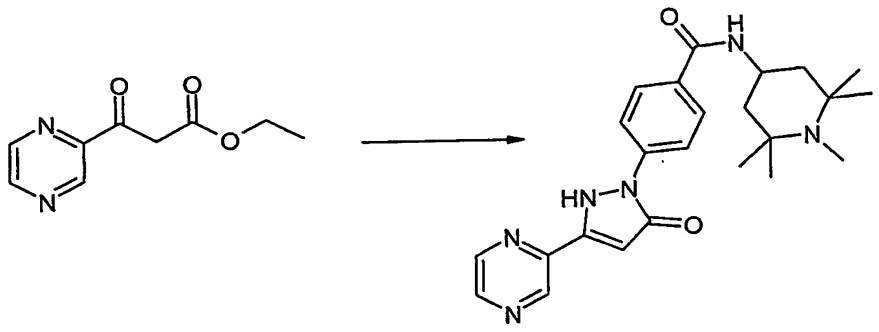
Step 4: Preparation of 3-Oxo-3-pyrazin-2-yl-propionic acid, ethyl ester.



To a stirred solution of diethyl malonate (1.25 ml, 1.32g) in THF (20 ml) under an atmosphere of nitrogen at -60°C was added nbutyl lithium (2.5 M, 9 ml) dropwise over 15 min, keeping the temperature constant. The reaction

became a cloudy white colour from the formation of the di-lithium salt then became yellowish. After 10 min, the reaction was cooled to -78°C, when a solution of pyrazine-2-carbonyl chloride (0.5 g, dark purple solution in THF (10 ml)) was added dropwise over 15 min. The reaction then warmed to -45°C and stirred for 1 h. The reaction was then poured into 1M HCl solution (35 ml) with stirring. This was transferred to a separating funnel, and extracted with CH_2Cl_2 (2 x 150 ml). The combined organic layers were then washed with sat. $NaCO_3$ soln (1 x 30 ml) and then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the product as a brown oil. Yield 0.65g, 45%.

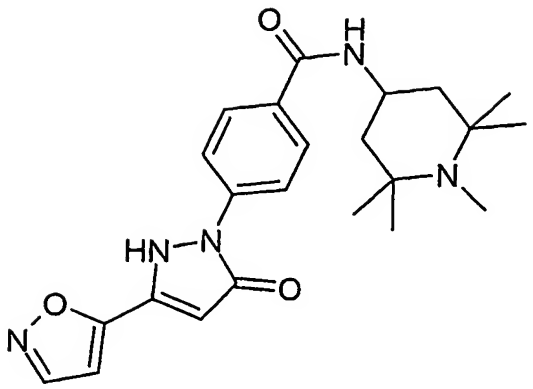
Step 5: Preparation of 4-(5-Oxo-3-pyrazin-2-yl-2,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide



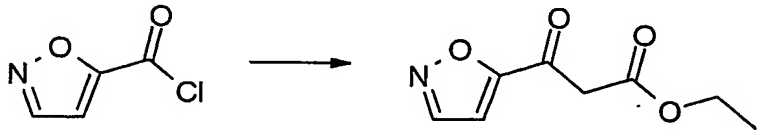
3-Oxo-3-pyrazin-2-yl-propionic acid, ethyl ester (78 mg) and 4-hydrazino-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide (141mg) were dissolved in ethanol (3.5 ml) and acetic acid (0.5 ml) and the solution stirred at 65 °C for 2h. Concentration *in vacuo* and purification by HPLC gave the expected product. LC/MS: main peak is product (m/z: 434)

Example 2

4-(3-Isoxazol-5-yl-5-oxo-2,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide

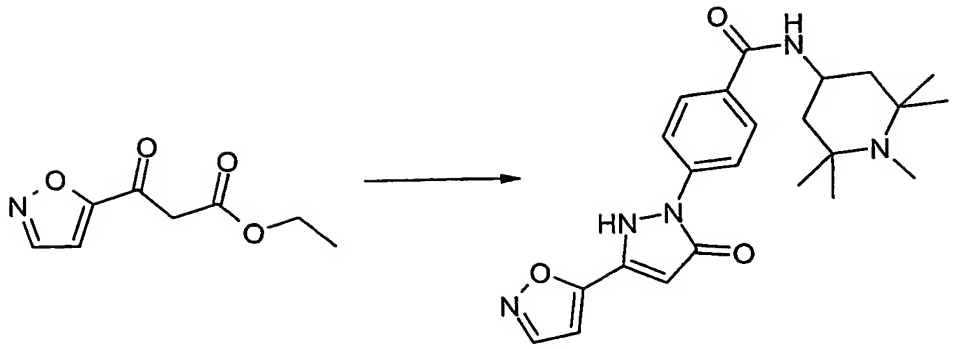


Step 1: Preparation of 3-Isoxazol-5-yl-3-oxo-propionic acid ethyl ester



To a stirred solution of diethyl malonate (2.6 ml, 2.74g) in THF (40 ml) under an atmosphere of nitrogen at -60°C was added *n*butyl lithium (2.5 M, 18.9 ml) dropwise over 15 mins, keeping the temperature constant. The reaction became a cloudy white colour from the formation of the di-lithium salt then became yellowish. After 10 mins, the reaction was cooled to -78°C, when a solution of Isoxazole-5-carbonyl chloride (1 g) in THF (10 ml) was added dropwise over 15 mins. The reaction then warmed to -45°C and stirred for 1 h, the solution had gone pale brown. The reaction was then poured into 1M HCl solution (50 ml) with stirring and extracted with CH_2Cl_2 (2 x 150 ml). The combined organic layers were washed with sat. $NaCO_3$ soln (1 x 30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the product as a pale oil which was used as such in the next step. Yield 1.1g, 35.1%.

Step 2: Preparation of 4-(3-Isoxazol-5-yl-5-oxo-2,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide

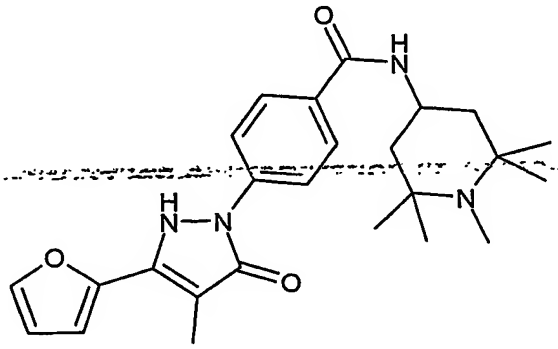


3-Isoxazol-5-yl-3-oxo-propionic acid ethyl ester (49 mg) and 4-Hydrazino-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide (93 mg) were dissolved into ethanol (2.5 ml) and acetic acid (0.3 ml) and the solution stirred at 65 °C for 2h. Concentration *in vacuo* and purification by HPLC gave the expected product. LC/MS: main peak is product (m/z: 424.3)

The compound of Example 2 had activity rating * in the HTRF assay described below.

Example 3

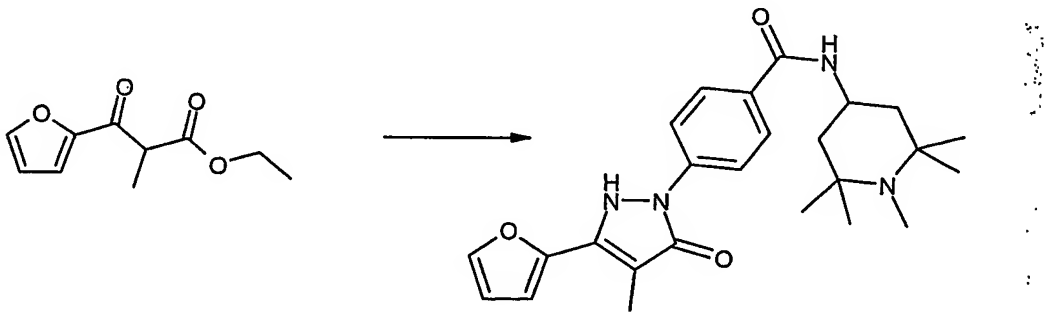
4-(3-Furan-2-yl-4-methyl-5-oxo-2,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide



Step 1: Preparation of 3-furan-2-yl-2-methyl-3-oxo-propionic acid ethyl ester

In a flask were placed ethyl 3-(2-furyl)-3-oxopropanoate (0.5g), iodomethane (0.14 ml), finely ground potassium carbonate (0.75g) and acetone (5 ml). The mixture was stirred at reflux for 2h. A further portion of iodomethane (0.9mmol, 0.056 ml) and potassium carbonate (0.9 mmol, 0.12g) were added and the mixture stirred at reflux for 1 h. The reaction mixture was filtered and concentrated under vacuum. Yield (0.5g, 93%).

Preparation of 4-(3-Furan-2-yl-4-methyl-5-oxo-2,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide

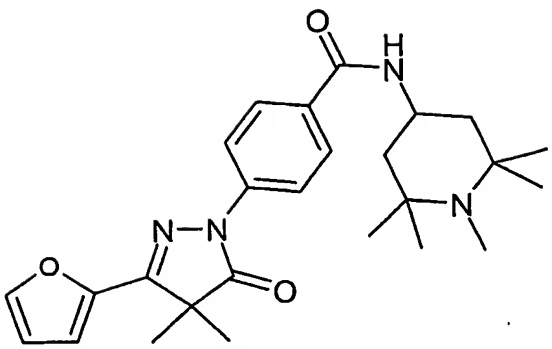


3-furan-2-yl-2-methyl-3-oxo-propionic acid ethyl ester (49 mg) and 4-Hydrazino-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide (85 mg) in 0.5 ml of acetic acid were heated up at 65 °C for 2h. Concentration *in vacuo* and purification by HPLC gave the expected product. MH+ = 437.3

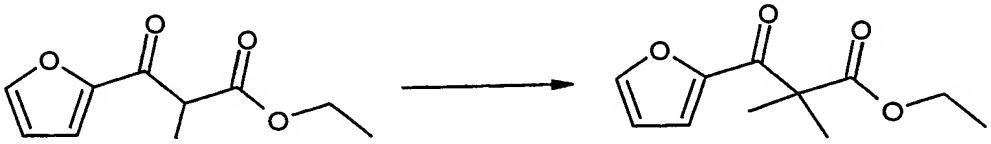
The compound of Example 3 had activity rating * in the HTRF assay described below.

Example 4

4-(3-Furan-2-yl-4,4-dimethyl-5-oxo-4,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide

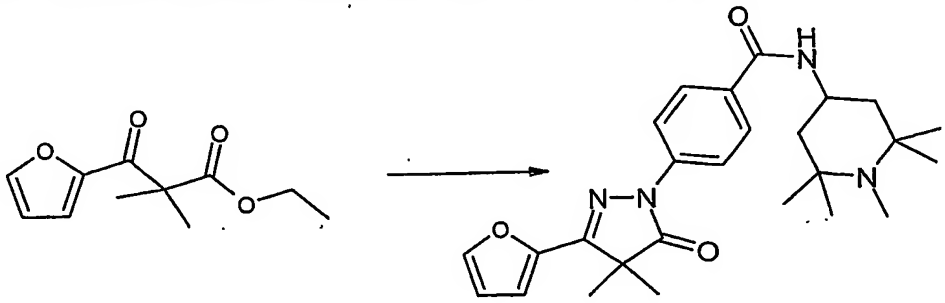


Step 1: Preparation of 3-Furan-2-yl-2,2-dimethyl-3-oxo-propionic acid ethyl ester



3-furan-2-yl-2-methyl-3-oxo-propionic acid ethyl ester (49 mg) was added sodium ethoxide (0.22 ml) and 0.5 ml ethanol. A solid precipitates. The solution was stirred at room temperature for 1h, iodomethane was added and the suspension stirred at room temperature for 3 h. Concentration *in vacuo* and purification by HPLC gave the expected product.

Step 2: Preparation of 4-(3-Furan-2-yl-4,4-dimethyl-5-oxo-4,5-dihydro-pyrazol-1-yl)-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide



3-Furan-2-yl-2,2-dimethyl-3-oxo-propionic acid ethyl ester (53 mg) and 4-Hydrazino-N-(1,2,2,6,6-pentamethyl-piperidin-4-yl)-benzamide (85 mg) in 0.5 ml of acetic acid were heated up at 65 °C for 2h. Concentration *in vacuo* and purification by HPLC gave the expected product (MH+: 451.4)

Additional Examples

Further examples of compounds of the invention were synthesised by methods analogous to those of Examples 1 - 2 above. The structures of the synthesised compounds are shown in the following Table, together with their activity ratings in the HTRF assay described below.

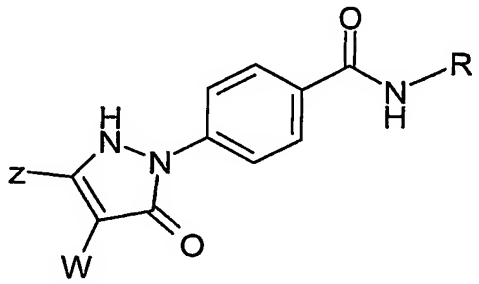
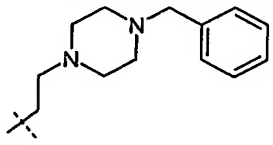
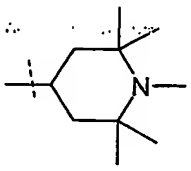
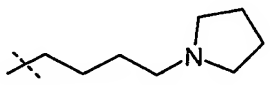
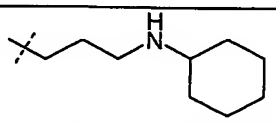
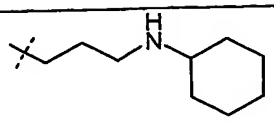
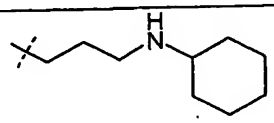
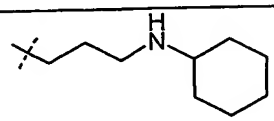
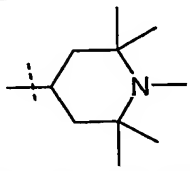
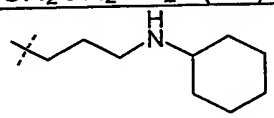
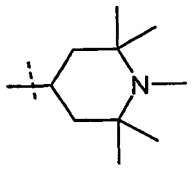
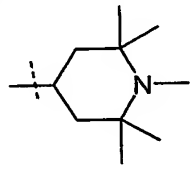
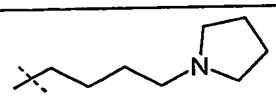
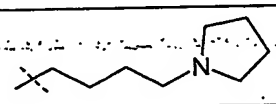
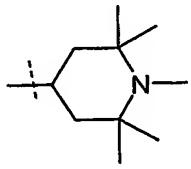
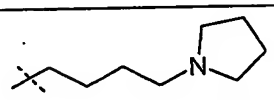
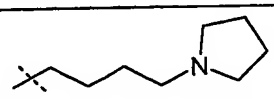
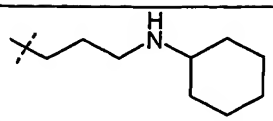
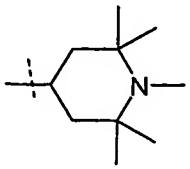
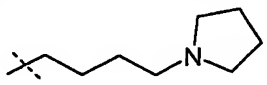
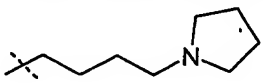
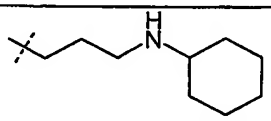
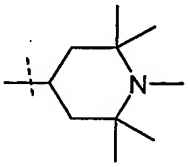
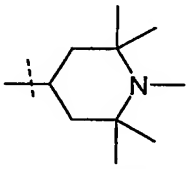


Table 1

Example	Z	W	R	MH+	Activity Rating
5	Ph	H	$CH_2CH_2CH_2N(Me)_2$	365.2	**
6	Ph	H		482.1	*
7	Ph	H		433.5	**
8	Ph	H		405.5	***
9	Ph	H		419.5	**
10	2-Pyridyl	H	$CH_2CH_2CH_2N(Me)_2$	366.5	***
11	2-furyl	H	$CH_2CH_2CH_2N(Me)_2$	355.4	***
12	3-Pyridyl	H	$CH_2CH_2CH_2N(Me)_2$	366.5	**

13	2-Pyridyl	H		420.5	**
14	2-furyl	H		409.5	***
15	3-Pyridyl	H		420.5	**
16	2-Pyridyl	H		434.6	***
17	3-furyl	H	$CH_2CH_2CH_2N(Me)_2$	355.5	**
18	3-furyl	H		409.5	***
19	2-furyl	H		423.6	***
20	3-furyl	H		423.6	**
21	2-furyl	H		395.6	**
22	3-furyl	H		395.6	**
23	3-Pyridyl	H		434.6	**
24	2-Pyridyl	H		406.5	***
25	3-Pyridyl	H		406.6	**
26	3F-phenyl	H	$CH_2CH_2CH_2N(Me)_2$	383.5	***

27	3F-phenyl	H		437.6	**
28	3F-phenyl	H		451.6	***
29	2-pyrazinyl	H		407.3	**
30	2-pyrazinyl	H	$CH_2CH_2CH_2N(Me)_2$	367.3	***
31	2-benzofuranyl	H		445.3	**
32	2-benzofuranyl	H	$CH_2CH_2CH_2N(Me)_2$	405.3	**
33	2-benzofuranyl	H		459.4	**
34	2-benzofuranyl	H		473.4	**
35	5-isoxazolyl	H		424.3	*

Assay Protocols

The use of BIAcore biomolecular interaction analysis

Biotinylated human CD80 (hCD80-BT) is a recombinant soluble form of a membrane bound receptor molecule (CD80) which binds to CD28 to initiate T cell activation. The interaction between CD80 and CD28 has been extensively investigated (Collins et al, 2002). Biotinlyated human HLA-A2-tax is the recombinant soluble form of a membrane bound receptor molecule that has been used in this example as a control protein, and is not expected to interact with the compounds.

The BIAcore S51™ system was used for screening the compounds of Examples 1-4 above. A series S sensor chip CM5 was docked onto the BIAcore S51™. Streptavidin was coupled to the carboxymethyl surface using standard amine coupling. The chip surface was activated with 0.2M EDC / 0.05M NHS, followed by binding of streptavidin (0.25 mg/ml in 10 mM sodium acetate pH 5.0) and saturation of unoccupied sites with 1 M ethylenediamine.

The BIAcore S51 sensor chip has two separate sensor spots for immobilisation of proteins. hCD80-BT was immobilised on the streptavidin-coated surface of one sensor spot until a response of approximately 3000 RU was observed. A protein to control for non-specific binding of the compound was immobilised on a second sensor spot. The control protein used for these experiments was a biotinylated, soluble form of the human HLA protein.

Dilution series of compounds (1000nM – 0.05nM) were prepared in running buffer (10 mM, pH 7.4, 150 mM NaCl, 0.005% P20; 5% DMSO).

BIAcore S51™ was run at a flow rate of 30 µl/min using running buffer. Compounds and DMSO standard solutions for correction of data for solvent effects were injected. Data were recorded automatically and were analysed using BIAcore S51 Evaluation software.

The interaction between CD80 and the endogenous protein ligand (CD28) is highly specific, but relatively weak, with a K_D of 4750 nM, and an off-rate of greater than 0.2 s^{-1}. The compounds of Examples 7, 11 & 18-21 have greater affinity and longer residence times on CD80 than CD28, having K_Ds of less than 100nM, and off-rates of $2x10^{-2}$, indicating that the pyrazolones will be able to compete effectively with the endogenous ligand. The pyrazolones showed no detectable interaction with the control protein.

References

Collins AV *et al.* (2002) Immunity 17, 201-210 "The interaction properties of costimulatory molecules revisited"

Inhibition of production of interleukin-2 (IL-2) by human Jurkat T cells.

Method

Human Raji cells were dispensed at a concentration of $2x10^5$ cells per well in RPMI-1640 medium supplemented with 10% fetal calf serum, 1% penicillin/streptomycin, 1% glutamine (RPMI medium) in a 96-well round bottom microtitre plate. Compounds under investigation (dissolved in 100% DMSO) were diluted to eight-fold the desired final concentration in RPMI medium and added to the required final concentration for a total volume of 200µl per well. After 20 minutes incubation at 37°C, Jurkat T cells were added at a concentration of $2x10^5$ cells per well. Monoclonal antibody to CD3 (UCHT1, R&D Systems) was added to the cultures at a final concentration of 1µg per ml, and where indicated, monoclonal antibody to CD28 (CD28.2, BD-Pharmingen) was also added at a concentration of 2.5µg per ml. Cells were cultured at 37°C for 5 hours, after which the plates were centrifuged and the supernatants harvested for IL-2 ELISA assay using the IL-2 Eli-pair kit (DIACLONE Research, Besancon, France) according to the manufacturers instructions.

By way of example, the compound of Example 26 gave 52% inhibition at 30 µM.

Homogenous Time Resolved Fluorescence Assay

The examples described above were tested in a cell free Homogenous Time Resolved Fluorescence (HTRF) assay to determine their activity as inhibitors of the CD80-CD28 interaction.

In the assay, europium and allophycocyanin (APC) are associated with CD28 and CD80 indirectly (through antibody linkers) to form a complex, which brings the europium and APC into close proximity to generate a signal. The complex comprises the following six proteins: fluorescent label 1, linker antibody 1,

CD28 fusion protein, CD80 fusion protein, linker antibody 2, and fluorescent label 2. The table below describes these reagents in greater detail.

Fluorescent label 1	Anti-Rabbit IgG labelled with Europium (1μg/ml)
Linker antibody 1	Rabbit IgG specific for mouse Fc fragment (3μg/ml)
CD28 fusion protein	CD28 - mouse Fc fragment fusion protein (0.48μg/ml)
CD80 fusion protein	CD80 mouse Fab fragment (C215) fusion protein (1.9μg/ml)
Linker antibody 2	GαMκ-biotin: biotinylated goat IgG specific for mouse kappa chain (2μg/ml)
Fluorescent label 2	SA-APC: streptavidin labelled allophycocyanin (8μg/ml)

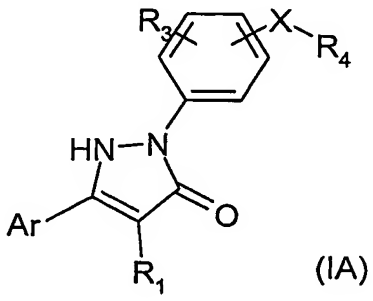
On formation of the complex, europium and APC are brought into proximity and a signal is generated.

Non-specific interaction was measured by substituting a mouse Fab fragment (C215) for the CD80 mouse Fab fragment fusion protein (1.9μg/ml). The assay was carried out in black 384 well plates in a final volume of 30μl. Assay buffer: 50mM Tris-HCl, 150mM NaCl pH7.8, containing 0.1% BSA (w/v) added just prior to use.

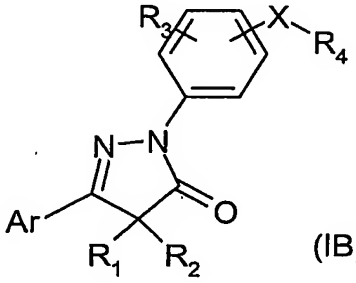
Compounds were added to the above reagents in a concentration series ranging between 100μM – 1.7nM. The reaction was incubated for 4 hours at room temperature. Dual measurements were made using a Wallac Victor 1420 Multilabel Counter. First measurement: excitation 340nm, emission 665nm, delay 50μs, window time 200μs. second measurement: excitation 340nm, emission 615nm, delay 50μs, window time 200μs. Counts were automatically corrected for fluorescence crossover, quenching and background. The EC50 activities of compounds tested are recorded as: EC50: * = >10 μM, ** = 1-10 μM, *** = <1 μM.

Claims:

1. A compound of formula (IA) or (IB) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof:



(IA)



(IB).

wherein

Ar represents an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group having from 5 to 10 ring atoms,

R_1 and R_2 independently represent H, or C_1-C_6 alkyl;

R_3 represents H; F; Cl; Br; -NO_2; -CN; C_1-C_6 alkyl optionally substituted by F or Cl; or C_1-C_6 alkoxy optionally substituted by F;

R_4 represents a carboxylic acid group (-COOH) or an ester thereof, or –C(=O)NR_6R_7, -NR_7C(=O)R_6, -NR_7C(=O)OR_6, –NHC(=O)NR_7R_6 or –NHC(=S)NR_7R_6 wherein

R_6 represents H, or a radical of formula –$(Alk)_m$-Q wherein

m is 0 or 1

Alk is an optionally substituted divalent straight or branched C_1-C_{12} alkylene, or C_2-C_{12} alkenylene, or C_2-C_{12} alkynylene radical or a divalent C_3-C_{12} carbocyclic radical, any of which radicals may be interrupted by one or more –O-, -S- or –N(R_8)- radicals

wherein R_8 represents H or C_1-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl, or C_3-C_6 cycloalkyl, and

Q represents H; $-CF_3$; -OH; -SH; $-NR_8R_8$ wherein each R_8 may be the same or different, or form a ring when taken together with the nitrogen to which they are attached; an ester group; or an optionally substituted aryl, aryloxy, cycloalkyl, cycloalkenyl or heterocyclic group; and

R_7 represents H or C_1-C_6 alkyl; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form a monocyclic heterocyclic ring having 5, 6 or 7 ring atoms; and

X represents a bond or a divalent radical of formula $-(Z)_n$-(Alk)- or $-$(Alk)-$(Z)_n$- wherein Z represents –O-, -S- or –NH-, Alk is as defined in relation to R_6 and n is 0 or 1.

2. A compound as claimed in claim 1 wherein R_1 in compounds (IA) and each of R_1 and R_2 in compounds (IB) is other than hydrogen.

3. A compound as claimed in claim 1 or claim 2 wherein R_4 represents a carboxylic acid group (-COOH) or an ester group of formula –COOR wherein R is methyl, ethyl n- or iso-propyl, n-, sec- or tert-butyl, or benzyl.

4. A compound as claimed in claim any of the preceding claims wherein R_6 represents a radical of formula $-(Alk)_m$-Q wherein m is 1, Alk is $-CH_2$-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH(CH_3)CH_2$-, or a divalent cyclopropylene, cyclopentylene or cyclohexylene radical, optionally substituted by OH, oxo, CF_3, methoxy or ethoxy, and Q represents hydrogen; $-NR_8R_8$ wherein each R_8 may be the same or different and selected from hydrogen, methyl, ethyl, n- or isopropyl or tert-butyl; a methyl, ethyl or benzyl ester; or an optionally substituted phenyl, phenoxy, cyclopentyl, cyclohexyl, furyl, thienyl, piperidyl, or piperazinyl group.

5. A compound as claimed in any of the preceding claims wherein R_7 represents hydrogen, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form a monocyclic heterocyclic ring having 5, 6 or 7 ring atoms;

6. A compound as claimed in any of the preceding claims wherein Ar is optionally substituted phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-furyl, 2-, or 3-thienyl, benzfur-2-yl, or benzthien-2-yl.

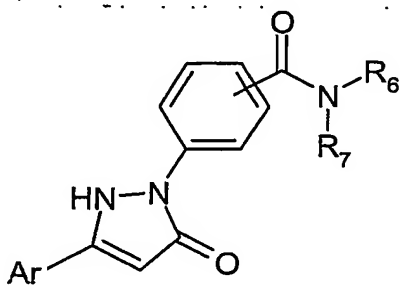
7. A compound as claimed in any of the preceding claims wherein Ar is substituted by F, Cl, methyl, methoxy, or methylenedioxy.

8. A compound as claimed in any of claims 1 to 5 wherein Ar is 3-fluorophenyl, or 2- or 3-furyl.

9. A compound as claimed in any of the preceding claims wherein R_3 is H, F, Cl, methyl, methoxy, or methylenedioxy.

10. A compound as claimed in any of the preceding claims wherein X is a bond, or a $-CH_2-$ or $-CH_2CH_2-$ radical.

11. A compound as claimed in claim 1 which is of formula (IC) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof:



((IC)

12. A compound as claimed in claim 11 wherein the radical $-C(=O)NR_6R_7$ is in the 4-position of the phenyl ring.

13. A compound as claimed in claim 11 or claim 12 wherein R_7 is hydrogen and R_6 is -AlkNR_8R_8 wherein the R_8 groups are as defined in claim 1.

14. A pharmaceutical or veterinary composition comprising a compound as claimed in any of claims 1 to 13 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

15. A compound as claimed in any of claims 1 to 13 for use in the treatment of conditions which benefit from immunomodulation.

16. The use of a compound as claimed in any of claims 1 to 13 in the manufacture of a medicament for the treatment of conditions which benefit from immunomodulation.

14. A method of immunomodulation in mammals, including humans, comprising administration to a mammal in need of such treatment an immunomodulatory effective dose of a compound as claimed in any of claims 1 to 13.

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